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REMARKS

Claims 13 and 16-22 are pending in the present application. Claims 13 and 16-22 stand rejected. No claims are amended or cancelled herein.

35 U.S.C. § 103(a)

Claims 13 and 16-22 stand rejected under 35 U.S.C. § 103(a), as being obvious over Stoute, *et al.*, in view of Davis, *et al.* (U.S. Patent No. 6,406,705). The Examiner alleges that Stoute, *et al.* teach a recombinant vaccine based on fusion of circumsporozoite protein and HBsAG (RTS,S) plus a "potent adjuvant." The Examiner further alleges that Stout, *et al.* teach the claimed invention except for the use of immunostimulatory CpG oligonucleotides. The Examiner then goes on to allege that Davis, *et al.* teach compositions comprising a synergistic combination of adjuvants (CpG and non-nucleic acid adjuvants) and antigen, further noting that the antigen can be a malarial antigen. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to prepare a composition comprising RTS,S and adjuvant CpG or CpG and aluminum salts. The Examiner also concludes that it would have been obvious to make a vaccine using CpG adjuvant since CpG induces Th1-type immune response. Finally, the Examiner alleges that based on the teachings of Stoute, *et al.* and Davis, *et al.* there would have been a reasonable expectation of success in preventing or ameliorating plasmodium infection in a patient by administering a composition based on the teachings of Stoute, *et al.* and Davis, *et al.*

The Applicants respectfully traverse this rejection. For a proper obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing *prima facie* with evidence or reasons that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. Both the suggestion [or motivation] and the reasonable expectation of success must be founded in the prior art, not in the appellants' disclosure." *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991) (citations omitted).

Stoute *et al.* disclose immunogenicity and protective efficacy studies with a hybrid malarial antigen, RTS,S, in the three following adjuvanted formulations:

"Vaccine 1" which contains the adjuvant alum/MPL (SBAS4);

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“Vaccine 2” which contains the adjuvant oil-in-water emulsion (SBAS3); and
“Vaccine 3” which contains the adjuvant oil-in-water emulsion together with MPL
and saponin (SBAS2), Stoute, *et al.* p87.

As disclosed in the section headed “Immunogenicity” on p88 of Stoute, *et al.*, antibodies against CS tandem-repeat epitopes developed in all subjects who received two or more doses. However, subjects who received two or three doses demonstrated significantly greater responses to Vaccines 2 and 3 compared to Vaccine 1. As disclosed in the section headed “Vaccine Efficacy” on p88, malaria developed in 7 of the 8 subjects treated with Vaccine 1 (i.e., efficacy 1/8), in 5 out of 7 subjects treated with Vaccine 2 (i.e., efficacy 2/7) and in 1 out of 7 subjects treated with Vaccine 3 (i.e., efficacy 6/7). Thus, Stoute, *et al.* teach that adjuvant can be very important in producing an immunogenic effect against malarial antigen. In fact, the vaccine comprising alum in combination with MPL (Vaccine 1) in Stoute, *et al.* demonstrates a lesser effect than the other two vaccines. Thus, there is no suggestion in Stoute, *et al.* to combine alum with any other adjuvant, particularly CpG, with a hybrid malarial antigen, as disclosed in the instant application.

Furthermore, Davis, *et al.* is directed to combinations of CpG with non-nucleic adjuvants; Davis, *et al.* does not disclose advantages of CpG alone with a malarial antigen. In addition, Davis, *et al.* merely recite a laundry list of bacterial, viral and parasitic antigens, but do not disclose any hybrid malarial antigens. In particular, Davis, *et al.* do not teach the use of a hybrid antigen such as RTS,S or RTS,S* in combination with CpG adjuvant. Thus, the Applicants respectfully submit that there is no teaching or suggestion in either reference, either alone or in combination, to combine hybrid malarial antigens with CpG adjuvant.

Even if, *arguendo*, there were a suggestion to combine CpG adjuvant with hybrid malarial antigens, neither Stoute, *et al.* nor Davis, *et al.* provide any expectation of success in developing a composition for raising an immune response. In fact, Stoute, *et al.* teaches that the choice of adjuvant can have significant effects on immune response and protection, with certain adjuvants enhancing a greater protective response than others. Thus, the skilled artisan would not have a reasonable expectation of success developing a composition capable of eliciting an immune response to a malarial antigen simply by combining any adjuvant and any malarial antigen. The Applicants respectfully submit that the Examiner has, therefore, not met either prong of her burden under *In re Vaeck*.

Claims 13 and 17-21 also stand rejected under 35 U.S.C. § 103(a), as being obvious over Stoute, *et al.*, in view of Krieg, *et al.* (U.S. Patent No. 6,207,646). The Examiner alleges

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that Stoute, *et al.* teach an antigen that is RTS,S while Krieg, *et al.* teach using CpG as an adjuvant. In particular, the Examiner notes that CpG is a “potent adjuvant” that induces a Th1-type response for protection against various pathogens such as parasites. The Applicants traverse this rejection and respectfully submit that, as noted above, Stoute, *et al.* teach that different adjuvants create different levels of protection and immunogenic effects when combined with RTS,S. The Applicants also point out that MPL is a Th-1 stimulating antigen (see, for instance, Wheeler, *et al. Allergy Immunology*, Vol 126(2)135-139 (2001), abstract only submitted herein with a Form 1449 for the Examiner’s convenience); however, Vaccine 1 demonstrated poor effects according to Stoute, *et al.* Furthermore, as the Applicants pointed out in their previous response, Krieg, *et al.* provide only a general disclosure that an antigen may be from a malarial parasite, and they do not disclose hybrid antigens at all. Thus, the Applicants submit that neither Stoute, *et al.* nor Krieg, *et al.* teach or suggest combining a hybrid malarial antigen with CpG. Furthermore, Stoute, *et al.* teach that Th-1 inducing adjuvants may have varying effects when combined with RTS,S. Thus, there is no teaching or expectation of success in either reference alone or combined to make a composition for raising immunogenic response comprising RTS,S or RTS,S* and CpG based on the teachings of Stoute, *et al.* and Krieg, *et al.*

Claims 13 and 17-19 and 22 stand rejected under 35 U.S.C. § 103(a), as being obvious over Stoute, *et al.*, in view of Raz, *et al.* (U.S. Patent No. 6,589,940). The Examiner alleges that Stoute, *et al.* teach that more “potent adjuvants” could be used with hybrid antigens. The Examiner then alleges that Raz, *et al.* teach compositions comprising immunostimulatory CpG oligonucleotides. The Examiner then concludes that based on Stoute, *et al.* and Raz, *et al.* it would have been obvious to one skilled in the art to prevent or ameliorate plasmodium infections. The Applicants traverse and submitted, as above and as noted previously, that Stoute, *et al.* teach the significance of adjuvant in eliciting an immune response to hybrid antigen in a malarial vaccine, while Raz, *et al.* fails to teach the combination of CpG with hybrid malarial antigens. Thus, neither of these references teach either alone or in combination that hybrid malarial antigen can be combined with a CpG adjuvant to create a composition capable of eliciting an immunogenic response.

Furthermore, the Applicants respectfully submit that the data disclosed in the instant patent application show the promise of CpG containing adjuvants in the absence of saponins with RTS,S antigen (see the Examples). Specifically, immunization with RTS,S and CpG or CpG and alum gave rise to HBsAg-specific CTL in mice. In rhesus monkeys, CpG alone

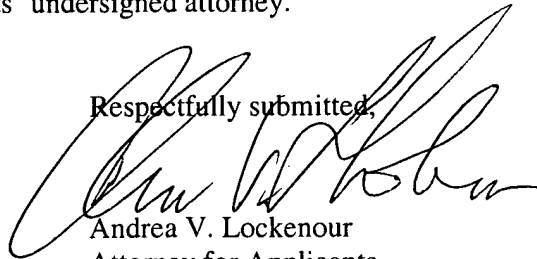
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gave rise to low level HBsAg specific antibodies while CpG combined with alum induced high titre antibodies as well as vigorous lymphoproliferative and IGn-gamma responses. Furthermore, the excellent results obtained with the combination of CpG and alum is especially surprising in view of the relatively poor results shown by Stoute, *et al.* for the alum/MPL example (Vaccine 1). Thus, the Applicants respectfully submit that the teachings of the instant application provide guidance to combine adjuvant comprising CpG in the absence of saponins with hybrid malarial antigens. It is only through hindsight that the Examiner is able to combine the individual elements of the cited art to reconstruct the elements of the instant claims.

The Applicants respectfully submit that in view of the forgoing remarks the Applicants have overcome the Examiner's rejection under 35 U.S.C. 103(a) and that rejection should be withdrawn.

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the cancelled claims, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited. If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,



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